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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/995,452	BENVENISTY ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-17 and 57-70* is/are pending in the application.

4a) Of the above claim(s) *57-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-17 and 59-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Response and Amendment, filed 7/11/07, has been entered. Claims 1, 11, 13, 16, 62, 63 are amended; claims 65-70 are newly added; claims 10, 18-56 are cancelled; 57-58 are not entered; claims 1-9, 11-17, 59-70 are pending and under current examination.

This action is **non-final**.

Information Disclosure Statement

Applicants' IDS, filed 9/12/07 has been considered.

Claim Objections

Claims 67, 69, 70 are objected to because of the following informalities: the claims recite "A" method of claim 65 (or claim 1). There is only one method in the independent claim. It is suggested that Applicants' amend the claims to recite The method of....

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-17, 59-70 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record, advance in the prior Office actions.

This is a new matter rejection. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Applicants' Arguments. Applicants' argue that the amendment does not introduce new matter into the as-filed disclosure, pointing to ¶43 of the specification. Thus, Applicants conclude that the present inventors were in possession of the concept of using a transfection reagent, such as cationic polymer, that provides improved results, when compared with electroporation, to transfect human ES cells. Applicants argue that this shows that one of skill in the art would recognize that Applicants had possession of the claimed invention and, "it does not matter that ExGen500 is the only example listed in the specification that meets these parameters." Applicants' argue that enablement is not the issue, but the issue is whether one of ordinary skill in the art would understand that the general concept that the invention includes the use of chemical transfection agents that have superior efficiency to electroporation when transfecting human ES cells. See pages 11-12 of the Response.

Response to Arguments. These arguments are not persuasive. The specification must provide support for Applicants' amendment. In the instant case, the specification only provides support for ExGen500 which produces the claimed result "a transfection efficiency greater than that obtainable by electroporation." MPEP §2163 states that, "New or amended claims which introduce elements or limitations which are not supported by the as-filed disclosure violate the written description requirement. See, e.g., *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971)." In the instant case the other transfection reagents (Fugene and Lipofectamine) did not produce greater relative transfection efficiency than electroporation alone. The Examiner acknowledges that this issue is not one of enablement, which is addressed separately. However, because the as-filed disclosure does not support that all of the reagents claimed have a transfection

efficiency greater than that obtained by electroporation, this would indicate that Applicants were not in possession of the claimed invention. It is reiterated that the other transfection reagents (Fugene and Lipofectamine) did not produce greater relative transfection efficiency than electroporation alone. Additionally, "a non-liposomal reagent" is not explicitly supported by ¶43 of the specification, which discusses "cationic polymers". Thus, in the context of the claimed invention as a whole, one of skill in the art would recognize that the specification only provides description for ExGen 500 as a transfection reagent that fulfills the limitations of the claims. The amendment to the claims that encompasses other transfection reagents that provide transfection efficiencies greater than that obtainable by electroporation are not described nor supported by the as-filed disclosure, and thus, constitute the introduction of new matter into the presently-filed disclosure.

Applicants' Arguments. Applicants' argue that they do not understand why the Examiner includes claim 7 in the rejection, as the claim specifies a cationic non-lipid polymer, as well as newly added claim 66. See page 12-13. Additionally, Applicants argue that claims 11-17, 69 and 70 specify using a cationic polymer, which is explicitly supported by ¶ 43 of the specification.

Response to Arguments. The Examiner responds that, in further analysis of the as-filed disclosure, the only support that is found for a reagent that produces a transfection efficiency greater than that obtainable by means of electroporation is ExGen 500. Therefore, it would be remedial to limit the claims to this specific reagent.

Written Description

The prior rejection of claims 1-9, 11-17, 59-63 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' amendment to the claims.

New Grounds of Rejection.

Claims 1-9, 11-17, 59-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new grounds of rejection.

The claims are directed to broadly using any cationic non-lipid polymer reagent, a non-liposomal reagent, and a cationic lipid polymer reagent to transfect hES cells, which results in a transfection efficiency greater than that obtainable by electroporation. The specification teaches ExGen provides a transfection efficiency greater than electroporation. The specification does not teach that Fugene or lipofectamine result in a transfection efficiency greater than electroporation. However, the genus of "cationic non-lipid polymer reagent", "non-liposomal reagent" and "cationic lipid reagent", which, when used as claimed, results in hES cells that have a greater transfection efficiency than that obtainable by electroporation, lacks a written description, and as such, there is no indication that Applicants had possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification, and are not conventional in the art as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the claimed invention in a detailed drawing, or by describing the invention with sufficient, relevant, identifying characteristics (as it relates to the claimed invention as a whole), such that one of skill in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the breath of the genus of "cationic non-lipid polymer reagent", "non-liposomal reagent" and "cationic lipid reagent" lacks a written description.

The skilled artisan cannot envision the detailed chemical structure of all of the reagents that are encompassed by the claims, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. The as-filed disclosure provides a single species, ExGen, in the genus of cationic non-lipid polymer reagents, that results in the claimed effect. "It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.,* 41 USPQ2d 1961, 1966 (CAFC 1997). See Purdue Pharma L.P. v. Faulding Inc. 230 F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed. Cir. 2000) noting that "with respect In re Ruschig 379 F.2d 990, 154 USPQ 118 (CCPA 1967) that Ruschig makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention." In order to satisfy written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure."

Adequate written description requires more than a mere statement that it is part of the invention, and a reference to a potential method of isolating it. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Enablement

Claims 1-9, 11-17, 59-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new ground of rejection.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Examiner's Comments. The scope of what is enabled in the claimed invention has been reconsidered. The Examiner addresses Applicants' comments, below, as they pertain to the existing aspects of the prior enablement rejection.

Operable Linkage to a Promoter. Applicants have stated it is not necessary for the polynucleotide that is being transfected be operably linked to a promoter, using a knockout construct as an example. Applicants argue that additionally, the polynucleotide itself may be a promoter, which is inserted to direct the transcription of an endogenous gene. Applicants argue that while a promoter may be present in the construct, it is not necessarily present. See pages 21-22 of the Response. The Examiner responds Applicants' remarks are persuasive with regard to this aspect of the claimed invention.

"By means of Electroporation". The claimed invention is fully not enabled for because the claim language recites that the transfection efficiency in hES cells, utilizing a cationic non-lipid polymer reagent, a non-liposomal reagent, and a cationic lipid agent, is greater than that that obtainable by means of electroporation. The phrase "means of electroporation" is not specifically defined by

the specification. The working examples do not provide the specific parameters that are used in order to determine transfection efficiency using electroporation, relative to the other claimed reagents. Although Figure 1 shows that using ExGen, Applicants found an increase in transfection efficiency, when compared to electroporation, there is no teaching to show that Fugene or Lipofectamine achieved the same results.

The ordinarily skilled artisan would recognize that the efficiency of electroporation depends on factors, such as the number of pulses and the intensity of the electric field. For example, http://www.cytopulse.com/electroporation.shtml (Accessed online, 9/27/07) provides general teachings on electroporation and teaches that the product of the pulse amplitude and pulse duration has to be above a lower limit threshold, and the number of pores and effective pore diameter increase with the product of amplitude and duration. Additionally, they teach that the upper limit for electroporation would result in cell damage or cell lyses. See 4th ¶. Thus, the "means of electroporation" of the claimed invention do not have defined parameters, and thus, encompass electroporation conditions wherein the lower limit threshold would not allow any cells to uptake DNA, and the upper limit threshold, wherein the cells would be killed. Certainly, if either of these limits were reached, one could achieve a greater transfection efficiency using cationic non-lipid polymers, non-liposomal reagents and cationic lipid agents. Thus, the claims as written provide no specific parameter with which to compare the other transfection reagents' relative transfection efficiency. It is further noted that Applicants' only have support showing that ExGen provides a transfection efficiency greater than means of electroporation, however, because the means of electroporation has not been defined, the Examiner cannot ascertain the proper scope of enablement, with regard to the parameters that are used to compare the two transfection methods.

Applicants' Arguments. Applicants argue that the specification is fully enabling because it teaches an assay for determining whether any agent is

substantially better than electroporation, pointing to ¶45. Applicants argue that many chemical transfection reagents are known in the prior art as alternatives to electroporation, and that the present specification teaches using other reagents that may have unexpectedly superior transfection efficiency. Applicants argue that while ExGen 500 is the only one that was explicitly shown to have this superior efficiency, the specification includes the concept that other chemical reagents will have such improved efficiency in hES cells, and particularly cationic polymer reagents. Applicants argue that in view of the assay disclosed, it would not require undue experimentation for one of ordinary skill to find additional such reagents. See pages 17-18 of the Response.

Response To Arguments. These arguments have been considered, but are not persuasive. The Examiner has addressed the issues of "means of electroporation" above. As stated in the prior Office actions, the breadth of the claims encompass using any of the transfection reagents (cationic non-lipid, non-liposomal, or cationic lipid), however, the specification teaches that only ExGen, a cationic, non-lipid polymer reagent, provides a greater transfection efficiency than that obtainable by electroporation. The other reagents, Lipofectamine™, FuGene™, provided efficiencies within the range of electroporation, not a greater efficiency than that obtained by electroporation. Thus, the specification does not provide enablement for any reagent other than ExGen to arrive at the claimed result. Although one of skill in the art might know various reagents that can be used in the claimed invention, it would require undue experimentation, with regard to the lack of parameters taught for electroporation, to determine which of the reagents would predictably arrive at a transfection efficiency greater than that of electroporation.

Accordingly, one of skill in the art would have had to practice undue experimentation to determine the specific, untaught parameters of electroporation, and then compare the other transfection reagents' relative transfection efficiency to these unknown parameters.

Claim Rejections - 35 USC § 112

The prior rejection of claim 16,under 112, 2nd ¶, is withdrawn in view of Applicants' amendments to the claims, which no longer recite "herpes simplex thymidine kinase".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicants' Arguments. Applicants argue that it is not understood why the Examiner states that the use of the cationic polymer reagent, and non-liposomal reagent, does not include the unexpected result of an efficiency greater than that of electroporation. Applicants argue that because all of the claims require this result, each reagent must possess the unexpected result. Applicants argue that no

limitation of a claim can be ignored when making an art rejection. See pages 18-19 of the Response.

Response To Arguments. The Examiner responds that the objective evidence of non-obviousness must be commensurate in scope with the evidence of record. The instant evidence of record shows that only cationic non-lipid polymer reagents provide a transfection efficiency greater than electroporation.

Additionally, the Examiner remarks that because there are no specific parameters, with regard to the electroporation methods (see above, Enablement, for a detailed discussion), the claims encompass electroporation conditions wherein the cells do not become transfected, or the cells are lysed or damaged in the process of electroporation. Thus, in these circumstances, it would provide a reasonable expectation of success that any of the claimed reagents would produce a transfection efficiency greater than that of electroporation. In short, absent specific conditions with regard to the electroporation techniques, it would have been obvious to combine the references of record.

It is noted that KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

Claims 1-4, 6, 8, 9, 11-16, 36, 59-61 and newly added claims 65, 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (U.S. Pat. No. 6,146,888, Reference AL of Applicants' Information Disclosure Statement, filed 3/26/03, cited previously) when taken with Ritter (Biochemica, No. 3, 1998, pages 47-49).

Applicants' Arguments. Applicants argue that Smith only relates to electroporation, and the present claims require a chemical transfection reagent, with results better than that of electroporation. See page 19 of the Response.

Response To Arguments. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In particular, Smith is used to show that various means can be used in order to introduce transgenes into stem cells. The Examiner has specifically provided Ritter to show that one of skill in the art would find it obvious to use the non-liposomal reagents, lipofectin and Fugene, to transfect cells, because Ritter teaches improvement of DNA transfer using liposome-mediated technologies (see 1st ¶). Thus, one of skill in the art would clearly modify the techniques of Smith to improve transfection yield, using reagents, such as those taught by Ritter.

Claims 1-4, 6, 9, 11-13, 15, 16 and newly added claims 65, 67-70 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* (cited above) when taken with Gibco BRL catalog (p. 350, 1992, cited previously).

Applicants argue that the Gibco catalog teaches LIPOFECTIN, however, Figure 1 of the present application does not fit the claim language. Therefore, the present claims do not encompass the use of LIPOFECTIN.

The Examiner responds that because there are no specific parameters, with regard to the electroporation methods (see above, Enablement, for a detailed discussion), the claims encompass electroporation conditions wherein the cells do not become transfected, or the cells are lysed or damaged in the process. Thus, in these circumstances, it would provide a reasonable expectation of success that any of the claimed reagents would produce a transfection efficiency greater than that of

electroporation. In short, absent specific conditions with regard to the electroporation techniques, it would have been obvious to combine the references of record.

Claim 5 and 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith when taken with Ritter as applied to claims 1-4, 6, 8, 9, 11-16, 36, 59-61 and newly added claims 65, 67-70 above, and further in view of Myers *et al.*

Applicants argue that Myers does nothing to cure the deficiencies of Smith and Ritter. The Examiner has responded to Applicants' arguments regarding Smith and Ritter above. This rejection is maintained.

Claim 17 stands rejected under 35 U.S.C. 103(a) as being unpatentable Smith when taken with Ritter as applied to claims 1-4, 6, 8, 9, 11-16, 36, 59-61 and newly added claims 65, 67-70 above, and further in view of Pascolo *et al.* (cited previously).

Applicants argue that claim 17 is depend from claim 11, and is allowable for the same reasons that claim 11 is allowable. Additionally, Applicants argue that Pascolo fills none of the deficiencies of the primary references. The Examiner has responded to the arguments regarding Smith and Ritter above. Accordingly, this rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Thaian N. Ton/
Primary Examiner
Art Unit 1632